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Review

The reflex sympathetic dystrophy syndrome: a review with special reference to chronic pain and motor impairments

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Reflex sympathetic dystrophy (RSD) is manifested by pain, vasomotor and trophic disregulation, and by various motor impairments. Its course shows a large variability, but an acute stage can roughly be discriminated from a chronic stage. The aim of this paper is to review the literature on RSD with regard to diagnosis and pathophysiology, in particular referring to chronic pain and motor impairments. It will be demonstrated that complementary investigations are helpful in making a definite diagnosis. RSD appears to be multicausal. In the acute stage, overproduction of toxic free radicals, sympathetic nervous system disregulation and neurogenic inflammatory reactions predominate. In the more chronic stage, a shift from peripheral to central mechanisms seems to take place. This centralization is probably an essential factor in the development and maintenance of both pain and RSD-associated motor impairments such as tremor, dystonia, increased muscle tone, muscle spasms and weakness. It is concluded that insight into the mechanisms underlying chronic pain and motor impairments in RSD has clear clinical implications, both for preventing disabilities and for developing rehabilitation strategies during the more chronic stages of RSD.

Das sympathische Reflexdystrophiesyndrom: Eine Literaturübersicht mit Schwerpunkt chronischer Schmerz und motorische Schädigungen

Die sympathische Reflexdystrophie (RDS – ‘reflex sympathetic dystrophy’) manifestiert sich in Form von Schmerzen, vasomotorischer und trophischer Fehlregulation sowie motorischen Schädigungen verschiedenster Art. Ihr Verlauf ist höchst unterschiedlich, jedoch lassen sich grob ein akutes und ein chronisches Stadium unterscheiden. Der vorliegende Beitrag will eine Literaturübersicht zum Thema RSD mit Blick auf Diagnose und Pathophysiologie geben, mit Schwerpunkt insbesondere auf chronische Schmerzen und motorische Schädigungen. Der Nutzen ergänzender Untersuchungen für die definitive Diagnosestellung wird aufgezeigt. In pathophysiologischer Hinsicht handelt es sich bei der RSD offensichtlich um ein multikausales Syndrom. Im Akutstadium stehen die Überproduktion toxischer freier Radikale, Dysregulation des sympathischen Nervensystems und neurogene entzündliche Reaktionen im Vordergrund. Mit zunehmender Chronifizierung scheint sich eine Verlagerung von peripheren hin zu zentralen Mechanismen zu vollziehen. Ein solcher Zentralisierungsprozeß ist vermutlich ein wesentlicher Faktor in der Entstehung und Aufrechterhaltung sowohl des Schmerzes als auch der mit der RSD einhergehenden

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motorischen Schädigungen wie Tremor, Dystonie, erhöhter Muskeltonus, Muskelspastik und -schwäche. Es wird gefolgert, daß das Wissen um die Mechanismen, die dem Schmerz und den motorischen Schädigungen bei RSD zugrunde liegen, eindeutige klinische Relevanz hat, sowohl für eine Prävention von Behinderungen als auch für die Entwicklung rehabilitativer Strategien in den stärker chronifizierten Stadien der RSD.

Syndrome du réflexe de dystrophie du sympathique.

Le réflexe de dystrophie du sympathique (RSD) se manifeste par de la douleur, des dérégulations vasomotrices et trophiques ainsi que par de nombreuses incapacités motrices. Son évolution montre de grandes divergences mais grossièrement on peut distinguer un état aigu et un état chronique. L'objet de cet article est faire une recension de la littérature portant sur le RSD en rapport avec le diagnostic et la physiopathologie en particulier pour tout ce qui touche la douleur chronique et les incapacités motrices. On démontrera que des investigations complémentaires aident à faire un diagnostic définitif. En ce qui concerne la physiopathologie le RSD apparaît comme un syndrome multicausal. Au stade aigu la surproduction de radicaux toxiques libres, de dérégulations du système nerveux sympathique et de réactions inflammatoires neurogéniques prédominent. Lors de l'état plus chronique, un transfert de la périphérie vers des mécanismes centraux semble se mettre en place. Un tel processus de centralisation est sans doute un facteur essentiel du développement et du maintien à la fois de la douleur et des handicaps moteurs associés au RSD tels que tremblement, dystonie, hypertonie musculaire, spasmes musculaires et fatigue. La conclusion montre que la compréhension des mécanismes en cause dans la douleur chronique et des incapacités motrices du RSD a des répercussions cliniques à la fois pour la prévention et pour le développement de stratégies de réadaptation lors du stade chronique du RSD.

El síndrome de la distrofia simpática refleja: una revisión particularmente centrada en el dolor crónico y en las deficiencias motoras.

La distrofia simpática refleja (DSR) se manifiesta con dolores, desarreglos vasomotores y tróficos, así como con varias deficiencias motoras. Cursa de forma muy variada, pero en términos generales la fase aguda se puede distinguir de una fase crónica. La finalidad de este artículo es pasar revista a lo publicado en torno a la DSR en relación con su diagnóstico y su fisiopatología, sobre todo refiriéndose al dolor crónico y a las deficiencias motoras. Se demostrará que los estudios complementarios son útiles para establecer un diagnóstico definitivo. En lo que se refiere a su fisiopatología la DSR se presenta como un síndrome multicausal. En la fase aguda, predominan el exceso de producción de radicales libres tóxicos, la desregulación del gran simpático y las reacciones neurógenas inflamatorias. En su estadio más crónico parece producirse un desplazamiento de los mecanismos periféricos hacia los centrales. Probablemente sea este proceso de centralización un factor esencial en el desarrollo y mantenimiento tanto del dolor como de las deficiencias motoras asociadas a la DSR, como son el tremor, la distonia, el incremento de tono muscular, los espasmos musculares y la debilidad. Se concluye que el conocimiento de los mecanismos subyacentes al dolor crónico y a las deficiencias motoras en la DSR tiene claras implicaciones clínicas, tanto para prevenir discapacidades como para desarrollar estrategias de rehabilitación durante las fases más agudas de la DSR.

Keywords: reflex sympathetic dystrophy; review; diagnosis; pathogenesis; pain; motor impairment

The reflex sympathetic dystrophy syndrome

The reflex sympathetic dystrophy syndrome (RSD) refers to a poorly understood and not well defined symptom complex formed by a combination of pain, trophic changes,

vasomotor disturbances and motor impairments. Usually it results from a minor injury. Minor causalgia, post-traumatic pain syndrome, Sudeck's atrophy, shoulder-hand syndrome, reflex neurovascular dystrophy and algodystrophy are some examples of disorders that are incorporated under the term RSD (Bruehl and Carlson, 1992). Given the variety of disorders ranged under the heading of RSD, it is not surprising that problems of definition and diagnostic ambiguities arise and that epidemiological data are hard to interpret. However, it can be stated that RSD is a significant problem worldwide with which many clinicians are faced (Schwartzman, 1992). Severe pain, occurring suddenly or progressively, is the most disabling feature and is experienced by the majority of patients (Doury, 1988). The severity of the pain seems disproportionate to the seriousness of the injury. It may have a burning character, mimicking a spreading neuralgia that is often called causalgia. Generally, it is accompanied by hyperpathia (lowered pain threshold and enhanced pain perception) and allodynia (pain from innocuous mechanical or thermal stimuli) and often by hyper- or hypoesthesia in a stocking- or glove-like distribution. Early in the clinical course of RSD, the pain may be sympathetically maintained and responsive to sympathetic blockade or sympathectomy. Later, it frequently becomes sympathetically independent (Schwartzman, 1992). If not responsive to treatment during the acute stage, the pain may become refractory to almost any form of treatment. It may then become a chronic problem with behavioural consequences as will be described later in this text. Trophic changes may include all structures from skin to bone including tendons, aponeuroses, muscles and joint capsules (Schwartzman, 1987). Nails may become brittle and hair loss or increased hair growth may occur. The skin may have a scleroderma-like appearance.

Vasomotor disturbances may manifest themselves in several ways (Doury, 1988). The red, warm and oedematous skin with vasodilation in the affected extremity reflects an inflammatory reaction. However, the skin may also be cold and mottled due to vasoconstriction with livedo reticularis, cold intolerance and induration.

Although epidemiological data on this matter are scarce, RSD-associated motor impairments (such as muscle weakness, tremor, dystonia, spasms and difficulty in initiating movements) form a well-known aspect of the syndrome. In the early stages of the disease, motor impairments may be present in very mild forms even without the patient being aware of them. During the later stages they may constitute, together with the pain, a major cause of disability. In a prospective study of 829 patients suffering from RSD, there was tremor in the affected arm in 49% and muscular incoordination in 54% of the subjects. Muscle spasms were present in 25% of the patients with RSD of longer duration, whereas 16% suffered from such severe weakness that no movements of the limbs were possible (Veldman *et al.*, 1993). In a study of 200 RSD patients, all patients in stages II or III exhibited some combination of weakness, spasms, tremor, increased tone, increased reflexes, difficulty in initiating movement or dystonia. Furthermore, the movement impairments may spread to other body parts, e.g. in a mirror-like distribution at the contralateral side (Schwartzman and Kerrigan, 1990).

Initiating events and course

RSD may be caused by a large range of eliciting events, ranging from (hardly recognized) minor injuries to surgical lesions; from non-traumatic diseases of the locomotor apparatus

(infectious, inflammatory, metabolic or neoplastic) to myocardial infarctions and pleuropulmonary diseases; from malignancies, endocrine diseases, the use of various drugs (barbiturates and antituberculous agents) to central neurological disorders such as traumatic spinal cord injury, acute stroke and multiple sclerosis (Cremer *et al.*, 1989; Davidoff *et al.*, 1989; Tepperman *et al.*, 1984). In about 25% of the adult cases, however, no inciting event can be identified, whereas in children this is even the rule (Goldsmith *et al.*, 1989; Kesler *et al.*, 1988; Sherry and Weisman, 1988; Silber and Majd, 1988).

RSD is supposed to progress according to three stages: acute (stage I), dystrophic (stage II) and atrophic (stage III) (Escobar, 1986). In stage I there is a history of persistent pain with hyperpathia, hyperaesthesia or allodynia in the affected part, with at least two of the following physical findings: increased hair or nail growth, oedema, livedo reticularis, temperature change, hyperhydrosis, or piloerection. In stage II dystrophic changes of soft tissue or nails or hair loss are added to the stage I symptoms. In stage III, as well as the features of stage I and II there is atrophy of skin, soft tissue, muscle and bone. However, these stages form a rather schematic and crude representation of the clinical course, because they are of variable length (ranging from weeks to years) and do not always emerge in a fixed order. In 5% of the RSD patients a cold extremity may even be the first symptom (Veldman *et al.*, 1993). Nevertheless, it appears that two extremes of a continuum can be distinguished: the acute stage during which inflammatory signs predominate and the chronic stage characterized by atrophy, chronic pain and motor impairments.

Diagnosis

The diagnosis of RSD is often solely based on the clinical presentation. In 1981 a classification system was proposed that distinguished four levels of probability of a positive diagnosis (Kozin *et al.*, 1981a). This classification is still being used. When pain and tenderness in the distal extremity are accompanied by swelling *and* vasomotor instability, the diagnosis of RSD is *definite*. If accompanied by swelling *or* vasomotor instability, the diagnosis is *probable*. RSD is considered *possible* when there is tenderness (but no pain) associated with vasomotor instability and/or swelling. In the case of merely unexplained pain and tenderness, diagnosis is *doubtful*. Recently presented criteria include exercise-induced occurrence of or increase in the following symptoms or signs: unexplained pain, oedema, changes in skin temperature or colour, or limited active range of motion. In addition, these signs and symptoms have to be present in an area larger than the area of primary injury, including the area distal to it (Veldman *et al.*, 1993). Despite the clinical relevance of RSD-associated motor impairments, they are hardly ever incorporated in clinical diagnostic criteria.

Each clinical sign of RSD may be suggestive of such diagnosis as septic, inflammatory, or tuberculous arthritis, metabolic arthropathy, tumor processes, osteonecrosis, arthrosis, stress fractures, etc. Therefore, although the diagnosis in its typical complete form is primarily a clinical one, it should be confirmed by laboratory, radiological and scintigraphic evidence (Houdenhove *et al.*, 1992). Complementary investigations may aid the evaluation of treatment and advance the diagnosis to an earlier phase, thus improving the therapeutic perspective.

Studies on biochemical constants in RSD are scarce. The non-specific parameters on inflammation (erythrocyte sedimentation rate (ESR), protein electrophoresis and fibrinemia) show no deviations. The absence of biochemical signs of inflammation is even considered as crucially important for a positive diagnosis (Doury *et al.*, 1981), which is remarkable because the stage I symptoms clearly suggest an inflammatory reaction. Hypercalcaemia, hypercalcuria and increased alkaline phosphatase levels have been described by Doury *et al.*, (1981) but are of no diagnostic importance, nor do they relate to the severity of RSD. Being a parameter of bone metabolism, the urinary excretion of hydroxyproline has received some attention. Hyperhydroxyprolinuria may support the diagnosis but is an inconstant finding because bone atrophy is not an obligatory symptom.

Only after considerable demineralization (30–50% of bone calcium) manifestations of RSD can be observed on plain radiographs. Radiological manifestations are not pathognomic and are usually preceded by clinical signs by 4 to 6 weeks. Sometimes bone demineralization does not appear until after several months. It may be absent during the entire evolution of the disease (Tepperman *et al.*, 1984). The typical pattern of spotty osteopenia is mainly seen in the epiphysis of the short bones of the hands and feet. Subchondral bone may virtually disappear, sparing the subchondral bony plate which thus may give a higher contrast. However, it may also result in less sharp bone contours of the joint. Subperiosteal resorption may cause thinning of diaphysial cortical layers. These radiographic signs should not be considered useful for early diagnosis but should be regarded as non-specific support for a positive diagnosis.

Since the 1970s several studies on radionuclide bone imaging techniques in the assessment of metabolic bone disease have been conducted. A growing number of these studies concern RSD. The three-phase bone scanning technique (TPBS) has proved to be a valuable diagnostic and treatment evaluation aid that is more sensitive and specific than plain radiography (Demangeat *et al.*, 1988; Kozin *et al.*, 1981b; Rico *et al.*, 1987; Weiss *et al.*, 1993). TPBS objectifies three parameters. Haemovelocity and bloodpool asymmetries are the two haemodynamic indices. They may demonstrate an asymmetrical perfusion of the limbs or an asymmetrical distribution of the bloodpool in either limb. Bone fixation is the third parameter and represents the bone calcium metabolism. Parallelling the clinical stages, three scintigraphic stages of RSD are distinguished. In stage I, bone fixation is invariably increased, and the haemodynamic indices are increased in 80% of the cases and normal in the rest. The bone fixation remains increased in the second stage, but the haemodynamic parameters may decrease, normalize or remain increased. In the third and last stage, bone fixation normalizes or decreases in about 60% of the subjects. The haemodynamic parameters are usually decreased in stage III reflecting vasoconstriction. Bone fixation is an important and sensitive diagnostic aid in stage I and helps to evaluate the persistence of the disease in stage III. Normalization of the haemodynamic indices in stages II and III may reflect therapeutic success. As argued before, a clear separation of RSD into three stages is a crude representation of its clinical course. The scintigraphic characteristics of these stages may overlap and therefore, even with TPBS, a clear division into three stages remains difficult. Usually in children, instead of an increased bone uptake, a diffusely decreased bone uptake at the symptomatic site can be observed (Goldsmith *et al.*, 1989). The cause of this remarkable contrast with adults has not yet been explained.

Pathophysiology

A historic overview

The symptom complex ranging under the term RSD has been known for over a hundred years. Mitchell (1872) introduced the term 'causalgia' (burning pain) and suggested that it is caused by peripheral as well as central pathophysiological mechanisms. He argued that 'inexplicable reflex transfers' in the spinal cord might be responsible for the severe pain experienced in tissues remote from the injured nerve area. Shortly after Röntgen's discovery of X-rays, Sudeck (1900) employed this new technique for studying the bony manifestations of several disorders. He was the first to link osteoporosis to RSD and to stress the inflammatory aspect of the syndrome. Leriche (1939) introduced the hypothesis of the 'vicious' circle in which peripheral mechanisms cause vasospasms and secondary ischaemic pain. On the basis of spinal reflexes, the sympathetic nervous system is activated through nociception, causing progression of vasospasms and ischaemia. Livingston (1944) expanded the concept of the vicious circle into a theory of 'reverberating circuits'. In Livingston's concept closed self-sustaining loops are triggered in the internuncial pool of the spinal cord by peripheral mechanisms. These self-sustaining loops spread to the ventral horns (causing muscle spasms), trigger an increase in sympathetic activity and activate spinal ascending neurons that subserve nociception. Doupe *et al.*, (1944) suggested a peripheral mechanism in which efferent sympathetic impulses depolarize afferent somatosensory fibres. Nathan (1947) indicated that somatosensory afferents are abnormally stimulated by efferents. He introduced the concept of artificial synapses that allow ephaptic transmission between efferent and afferent fibres. More recently, Melzack (1971) postulated that both causalgia and phantom pain are the result of a decreased inhibitory influence of a 'central biasing mechanism' in the brainstem reticular formation due to a lowered sensory input. As a result self-sustaining activity in closed neuronal loops increases at all neural levels. Melzack's theory differs from others in the assumption that a decreased sensory input and not an increased nociceptive afference is at the basis of spinal disregulation in RSD. Much resembling Livingston's reverberating circuits, Sunderland (1976) suggested a disregulation of the dorsal horn cells leading to self-sustaining hyperactive foci spreading along transmission pathways in the spinal cord ('turbulence hypothesis').

This short historical overview illustrates that most of the proposed concepts focus on pain perception and trophic disturbances through either peripheral or central mechanisms. Nevertheless, the theories of Leriche, Livingston, Melzack and Sunderland already embrace some interactionistic ideas. In the present paper an interactionistic concept is adopted and expanded to the pathophysiology of motor impairments. RSD is conceptualized as the result of a disturbed interaction between central and peripheral mechanisms leading to a centralization of pathological processes. In the acute stage with inflammatory signs, peripheral mechanisms predominate. In later stages, a gradual shift towards a disregulation of the central nervous system takes place. This process of centralization is assumed to be at the basis of chronic pain, trophic disturbances and RSD-associated motor impairments. This interactionistic viewpoint will be further elaborated in the following sections, starting with the pathophysiology of pain and trophic changes (Fig. 1), followed by the mechanisms underlying motor impairments (Fig. 2). It will become clear that this differentiation is somewhat artificial and made for a pragmatic reason. For

the same reason, peripheral mechanisms are consistently discussed before central mechanisms.

Pain and trophic disturbances in RSD, a peripheral notion; I: toxic free radicals

An important peripheral aspect of RSD, viz the inflammatory aspect of the affected area, has already been stressed by Sudeck (1900). This idea received little attention until the notion of RSD as an inflammation could be linked to the hypothesis that toxic free radicals can mediate inflammatory reactions (Goris *et al.*, 1987). Free radicals possess an unpaired electron and can be considered as fragments of molecules that generally are very reactive. Oxygen and its radical derivatives (superoxide and the hydroxyl radical) are important examples of free radicals. They are produced continuously in cells either as accidental by-

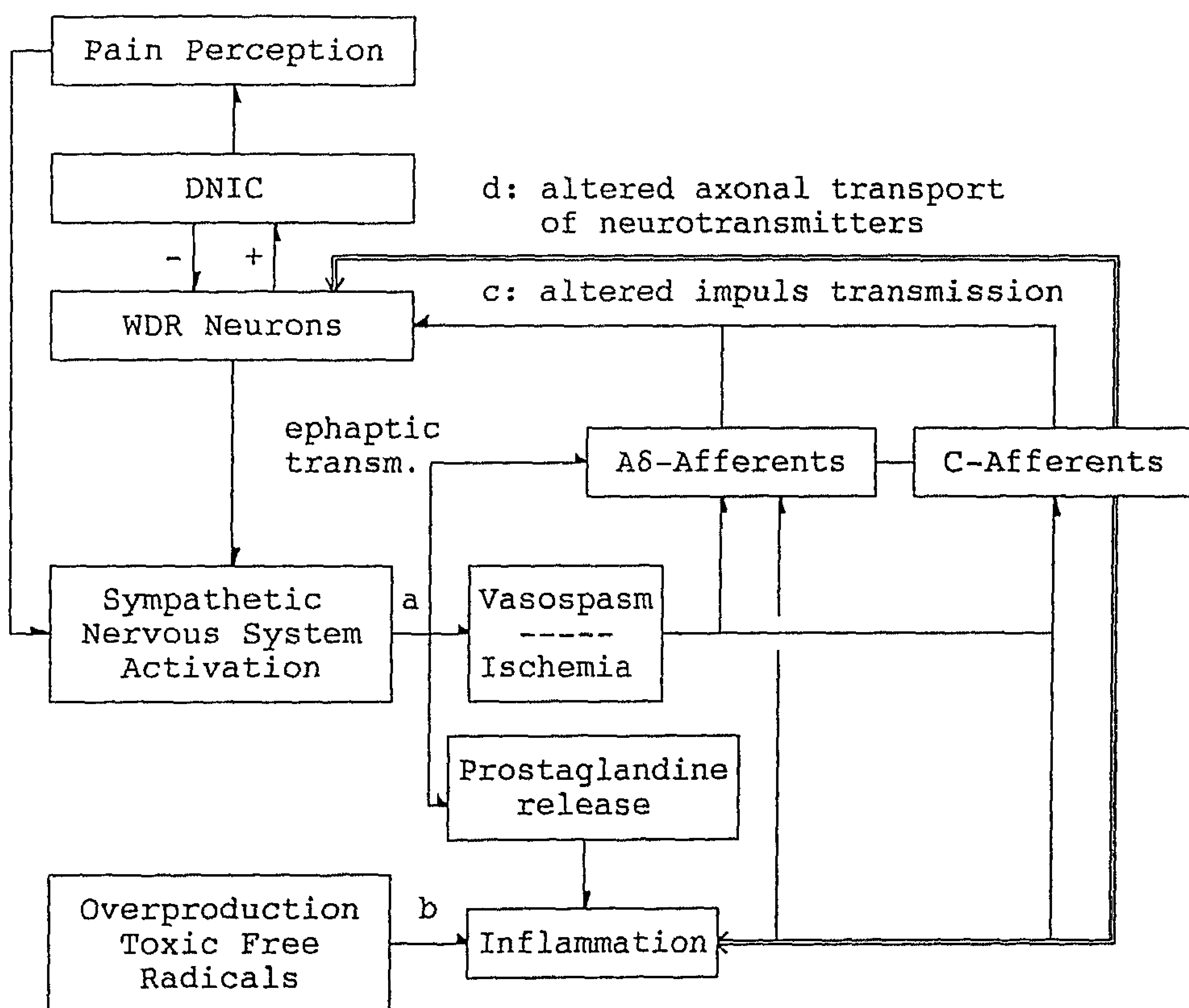


Fig. 1. Depolarization of myelinated A- δ and unmyelinated C-afferents is modulated by the sympathetic nervous system – (a) Ephaptic transmission, changed micro-environment of primary afferents due to vasospasm and prostaglandine release – and through an inflammatory reaction. The inflammatory reaction is mediated by an overproduction of toxic free radicals (b) or by a neurogenic release of inflammatory substances caused by altered axonal transport of neurotransmitters (d). Axonal transport of neurotransmitters is antero- and retrograde (double bars). Therefore, besides a peripheral neurogenic inflammatory reaction, this mechanism may cause sensitization of spinal wide dynamic range (WDR) neurons. When stimulated, WDR neurons activate the diffuse noxious inhibitory controls (DNIC) that serve as an amplifier of a nociceptive stimulus (c). Allodynia is explained by stimulation of sensitized WDR neurons by innocuous activation of A-mechanoreceptors.

products of metabolism or deliberately, e.g. during phagocytosis, in which case their function is to suppress noxious stimuli by activating the immune response (Fantone and Ward, 1982; Cheeseman and Slater, 1993). However, reactive free radicals formed within cells can oxidize biomolecules and lead to cell death and tissue injury. Hence, a well-controlled balance between the production and breakdown of free radicals is critical in maintaining the integrity of cells and tissues. It has been suggested that excessive production of free radicals can be responsible for cell and tissue damage and progression of the inflammatory reaction in RSD. The fact that a number of patients with inflammatory signs have been successfully treated with radical scavengers such as mannitol and dimethylsulphoxide is a preliminary support of this notion (Goris, 1988). However, free radicals are extremely reactive and short-lived. Currently available techniques to measure free radicals are limited to semiquantitative assays of damage to biomolecules, which is the main reason that a causal role of free radicals in RSD is yet hard to verify (Holley and Cheeseman, 1993).

Pain and trophic disturbances in RSD, a peripheral notion II: the sympathetic nervous system

Because of the vasomotor disturbances and positive reactions to sympathectomies, the sympathetic nervous system is thought to play an important pathophysiological role in RSD. There is ample evidence that in lower vertebrates efferent sympathetic activity modulates depolarization of myelinated (A δ) and unmyelinated (C) cutaneous afferents (Jänig, 1985, 1990). Three ways in which sympathetic post-ganglionic nerve fibres may affect cutaneous afferent fibres have been described (Jänig, 1985). The first refers to ephaptic transmission. This abnormal cross-talk between fibres may occur among cutaneous afferents but also between autonomic postganglionic efferent fibres and cutaneous afferents. The second refers to the fact that noradrenaline-releasing post-ganglionic sympathetic axons change the micro-environment of primary afferents, thus causing altered chemosensitivity. Thirdly, there is evidence that noradrenaline acts presynaptically on α -2 adrenergic receptors on the sympathetic post-ganglionic terminals (Levine *et al.*, 1986). This causes a release of prostaglandin that contributes to an inflammatory reaction and leads to decreased thresholds of cutaneous afferents for nociceptive stimuli. A study by Arnold *et al.*, (1993) provided *in vivo* evidence of increased responsiveness of venous α -adrenoreceptors to locally infused noradrenalin in limbs affected by RSD. This increased responsiveness was also present in the contralateral unaffected extremity, which is compatible with the clinical finding that RSD may spread from one affected limb to other extremities. This mirror distribution of increased responsiveness to infused noradrenaline supports the notion that central changes in autonomic outflow are relevant in RSD. RSD may spread from a lower extremity to an upper extremity or vice versa, which suggests that the central influence is not confined to one or adjacent segments of the spinal cord, but that more rostral structures can be involved (Teasell *et al.*, 1994).

Pain and trophic disturbances in RSD, and interactional notion: neurotransmitters

Several neurotransmitters such as excitatory amino acids (L-glutamate, L-aspartate and L-homocysteate), neurokinins (substance P, neurokinin A, neurokinin B) and other peptide neurotransmitters such as calcitonine gene-related peptide and vasoactive intestinal peptide

are involved in linking peripheral (inflammation and sympathetic activity) to central mechanisms (Roberts, 1986). In the case of nerve injury, not only the impulse transmission between the peripheral and central nervous system is disrupted, but also anterograde and retrograde axonal transport of neurotransmitters. These transmitters are produced in the spinal ganglia and transported both to the spinal cord and to the periphery. The axonal transport routes are important in establishing and maintaining peripheral and central connections of afferent and efferent fibres. In particular the unmyelinated C-afferent fibres subserve this trophic function. Altered antero- and retrograde axonal transport may result in a changed state of axons, e.g. sprouting, ephaptic transmission, partial deafferentation and even permanent cell loss. These processes may lead to peripheral reactions such as neurogenic inflammatory reactions (local vasodilatation, chemotaxis and extravasation due to the local influence of the neurotransmitters) as well as central changes such as shifting of receptive fields in neural networks and unmasking of synaptic connections. Transneural chemical changes spreading from peripheral afferents to the spinal cord and even to the supraspinal regions have been reported in the case of deafferentation (see Ribbers *et al.*, 1989; Davis, 1993; Brasil-Neto *et al.*, 1993). This finding underlines that the central nervous system is adaptive to peripheral influences. Within this perspective, Roberts (1986) formulated a hypothesis in which wide dynamic range (WDR) neurons in the dorsal horn of the spinal cord serve as an interface between central and peripheral processes. Cutaneous afferents (unmyelinated C-afferents and myelinated A δ -afferents) project both to nociceptor-specific and to WDR neurons. The axons of the WDR neurons ascend to supraspinal centres to identify and localize pain. WDR neurons are in fact convergent. The centres of their receptive fields are responsive to noxious and innocuous stimuli, whereas the peripheral areas are only responsive to noxious stimuli (le Bars and Chitour, 1983). Depolarization of C-afferents induces sensitization of WDR neurons through axonal transport of neurotransmitters. Enlarged cutaneous receptive fields, a lowered threshold to fire and a greater responsiveness are the neurophysiological manifestations of central sensitization (Schwartzman, 1992). Sensitized WDR neurons may cause pain perception after innocuous stimulation of A-mechanoreceptors explaining allodynia. Spontaneous pain results from altered central processing and is maintained dynamically by an ongoing peripheral input such as inflammatory reactions and sympathetic activity (Graceley *et al.*, 1992). WDR neurons activate the diffuse noxious inhibitory controls (DNIC) which seem to be an analogue of Melzack's central biasing mechanism (Roberts, 1986). When activated, the DNIC inhibit all background activity of the remaining spinal and trigeminal WDR neurons. In reducing the background firing, the DNIC allow the extraction of a meaningful nociceptive message from non-specific activities of WDR neurons. The DNIC thus serve as a filter or amplifier with an important alarm function, in which psychological mechanisms such as arousal or mood disorders may be involved.

Motor impairments in RSD

The pathophysiology of RSD-associated motor impairments is still a matter of controversy. Much like the discussion on pain and trophic disturbances in RSD, the discussion on motor impairments focuses on such mechanisms as oxydative stress, sympathetic nervous system dysregulation, the excitatory influence of neuropeptides on spinal motor neurons as well as possible supraspinal mechanisms. Finally, the possibility of a psychopathological basis is

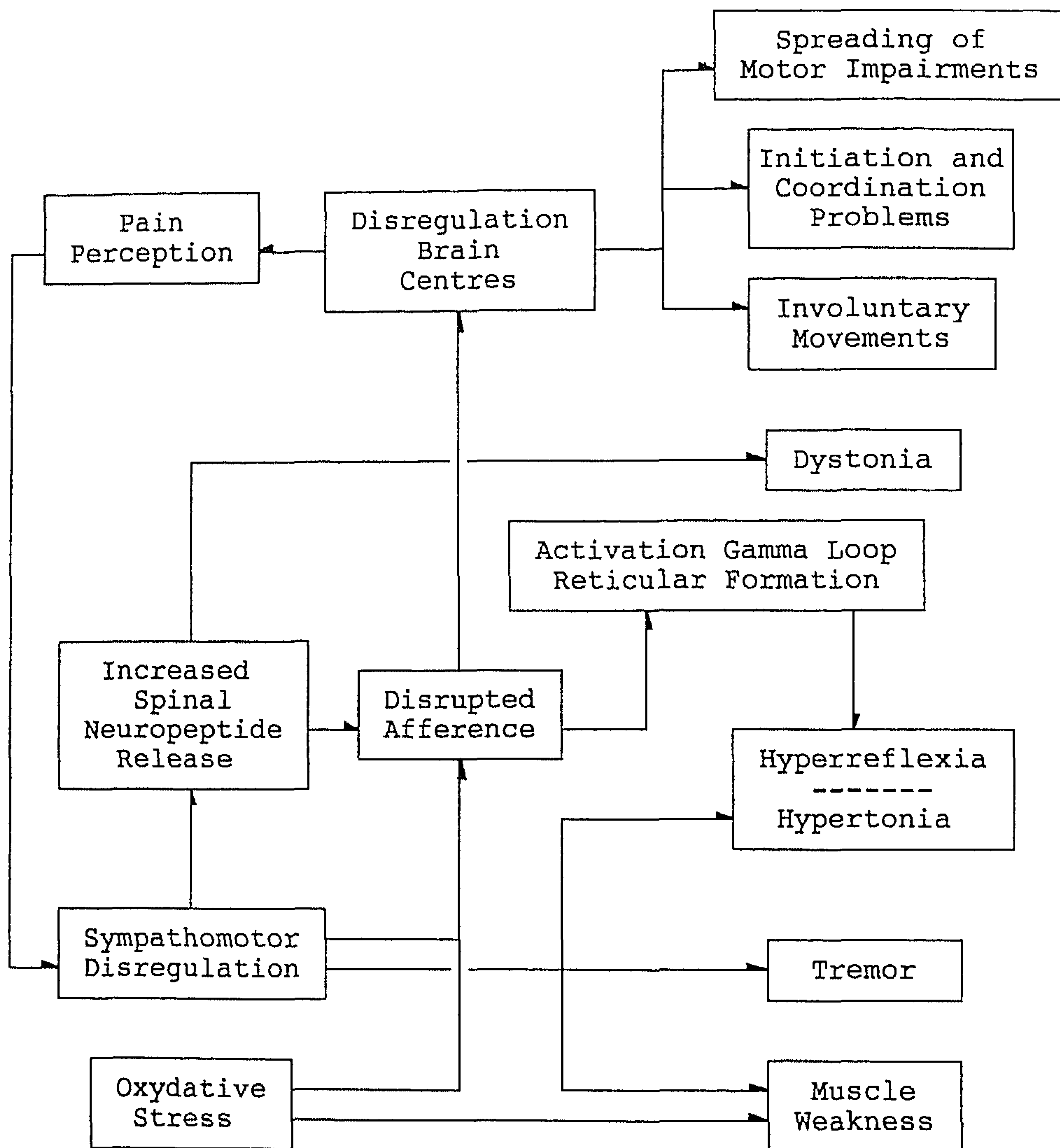


Fig. 2. Schematic overview of the mechanisms that underlie RSD-associated motor impairments (for discussion see text).

mentioned. The remaining part of this paper will further elaborate the possible causes of RSD-associated motor impairments (see Fig. 2).

Motor impairments in RSD, a peripheral notion: oxydative stress

It has recently been argued that peripheral oxydative stress due to impaired oxygen extraction in the affected extremity explains for the loss of motor control in RSD. Heerschap *et al.* (1993) investigated the lower leg skeletal muscles at rest in 11 RSD-patients by ^{31}P -nuclear magnetic resonance spectroscopy. The results were compared with similar investigations of unaffected legs in patients and volunteers. An increase in average

tissue pH in the muscles of the affected legs and an increase in the average inorganic phosphate/phosphocreatine ratio (P_i/P_{Cr}) was observed. These observations are attributed to oxydative stress in the limbs affected by RSD.

However, although oxidative stress may explain an increase in pain during movement and perhaps muscle weakness, it remains hard to understand how it may cause dystonia, tremor, involuntary movements, spasms or spreading of motor impairments to other body parts.

Motor impairments in RSD, an interactional notion: sympathomotor interaction and neuropeptides

Dysregulation of the sympathetic nervous system may also be a possible cause of motor impairments in RSD. Sympathetic innervation of intrafusal and extrafusal fibres of the muscle spindle and ventral horn efferent fibres has been demonstrated (Selkowitz, 1992) and may underlie the sympathomotor interaction. Sympathomotor dysregulation may be at the basis of muscle weakness, tremor, increased muscle tone, increased reflexes and dystonia in RSD.

Yokata *et al.* (1989) described four RSD patients with muscle weakness that improved dramatically after sympathetic blocks and worsened by catecholamine loading. This was thought to be due to abnormally increased sympathetic tone and was called 'sympathetic motor paresis'.

Tremor in RSD is regarded as an enhanced physiological tremor that is sympathetically maintained or even induced and that may normalize after sympatholytic interventions (Deutsch *et al.*, 1991). It has been argued that sympathetic sensitization of muscle spindles is at the basis of tremor in RSD. Sensitized muscle spindles cause a gain of proprioceptive reflexes. Enhanced proprioceptive reflexes are a major peripheral input causing synchronous discharges of motor units and thereby enlarged tremor amplitudes (Stein and Lee, 1981).

Besides muscle weakness and tremor, other RSD motor manifestations such as increased muscle tone, increased reflexes and dystonia may also be sympathetically induced (Schwartman, 1992). Firstly, sympathetic nerve stimulation increases the firing rate of muscle spindle afferents, which increases muscle tone and deep tendon reflexes. Secondly, as argued before, sympathetic stimulation modifies the activity of myelinated and unmyelinated cutaneous afferents, which activates the gamma loop via the reticular formation, thus increasing muscle tone. Thirdly, sympathetic stimulation of unmyelinated afferents causes altered axonal transport of neuropeptides. Neuropeptides, such as substance P, are transported to different parts of the spinal cord and produce long-lasting depolarization of anterior horn cells *in vitro*. The interaction between substance P and the sympathetic nervous system is thought to underlie the intense and prolonged depolarization of anterior horn cells causing dystonia in RSD (Deutsch *et al.*, 1991; Schwartzman, 1992).

Motor impairments in RSD, an interactional notion II: centralization

The autonomic nervous system may play a crucial role in mediating RSD-associated motor impairments. However motor impairments may persist after the recovery of autonomic dysregulation and may become irresponsive to sympathetic blockades. Furthermore, RSD motor impairments may spread beyond the original site in a hemiplegic, transverse or

crossed distribution. This spreading of motor impairments cannot be explained on the basis of a peripheral origin and is also difficult to relate to invoking segmental changes in the spinal cord. Bathia *et al.* (1993) argued that, at the spinal level, a hemiplegic distribution can only be explained on the basis of propriospinal pathways that control axial muscles, whereas RSD motor impairments are usually restricted to the distal extremities. The same is true for a possible site of origin of motor impairments at the brainstem, because brainstem motor pathways also control the axial muscles. Hence, it appears that in an early stage the sympathomotor interaction is fundamental, whereas in later stages higher central mechanisms may be involved.

Indeed, there is some support for the notion that the process of centralization expands to higher brain structures. For instance, the case reports by Marsden *et al.* (1984) and Robberecht *et al.* (1988) provide direct support for the possibility of cerebral involvement. Firstly, Marsden *et al.* (1984) reported a patient suffering from RSD after fracturing a metacarpal bone in a fall. One year after the injury, abnormal involuntary movements of the hand developed, initially intermittently but over a few months only disappearing during sleep. After failure of treatment with various drugs and a stellate ganglion block, thermocoagulation of the thalamic ventral intermediate nucleus was performed. This procedure abolished the motor impairment and reduced the pain. Secondly, some additional support for cerebral involvement is based on electro-encephalography. Altered cortical potentials preceding involuntary movements in RSD have been registered (Robberecht *et al.*, 1988). In one patient there was even no difference between the cortical potential preceding the involuntary movement and the readiness potentials occurring before voluntary flexion of the contralateral extremity.

Although these studies are not conclusive, they indicate that supraspinal and even cerebral mechanisms may be involved. It can therefore be hypothesized that cerebral involvement after peripherally induced motor impairments is the final state of a progressive centralization process. This is certainly not a new idea. Jankovic and van der Linden (1988) described 23 patients with focal dystonia, tremor or both occurring after acute peripheral injury. Ten of these patients had RSD. Those with psychogenic motor impairments were excluded. In addition to a detailed neurological examination, neurophysiological investigations including nerve conduction velocities, electromyography and somatosensory evoked potentials were performed. They concluded that central mechanisms are fundamental in RSD-associated motor impairments and that 'a specific central susceptibility to altered afferent input may be required for the movement disorders to occur'. They assumed that, e.g., perinatal problems and the use of neuroleptic medications may lead to such a central susceptibility. Schott (1981, 1985, 1986) has also emphasized the role of central mechanisms in motor impairments after peripheral trauma in a syndrome called 'painful legs and moving toes'.

Outside the field of RSD research there is growing evidence of a strong central-peripheral interaction that may underlie a process of centralization after peripheral injury. Reorganization of spinal and cerebral neural networks due to altered input has been observed after sectioning peripheral nerves, after anaesthetic blocks, after amputation of body parts and after section of the dorsal roots of peripheral nerves (Kaas *et al.*, 1983; Cohen *et al.*, 1990; Hall *et al.*, 1990; Topka *et al.*, 1991; Brasil-Neto *et al.*, 1992). Reorganization at a spinal level has already been reported by Wall (1980) who sectioned peripheral nerves depriving a population of spinal cord cells from their normal input. It was shown that large numbers of cells in a region of the cord that were normally

dominated by afferents from the foot and the toes began to respond to other areas of the leg in several days or weeks after the peripheral deafferentation. Levine *et al.* (1985) emphasized the neural basis that underlies the spreading of acute inflammation from a site of injury to a remote uninjured site in which the spinal cord, nociceptive afferents and sympathetic efferents are involved. He described that in rats an injured hind paw elicited a contralateral inflammatory response even though pure humeral mechanisms were excluded. They referred to this phenomenon as 'reflex neurogenic inflammation'. As for the role of the nervous system in mediating inflammatory reactions, neuronal plasticity following tissue injury has also been reported by Dubner and Ruda (1992).

Merzenich and co-workers focused their attention on cerebral plasticity. They showed that the spatial representation of body parts on the primary somatosensory cortex of monkeys can be significantly changed by manipulations of peripheral input (Merzenich and Kaas, 1982; Merzenich *et al.*, 1983). In a series of experiments, they sectioned median nerves in monkeys and showed that immediately after this section most of the cortical territory, that was previously activated by the cut nerve, became unresponsive to stimulation. Besides this neural decay, in most monkeys small islands within the 'silent' cortex became responsive to stimulation from neighbouring dermal areas. Several weeks after the nerve section, the previously silent cortical regions were totally reorganized now responding to input from intact peripheral nerves. Identical cortical reorganizations have been observed after amputation of digits of the hands of racoons (Carson *et al.*, 1981). In humans, Pascual-Leone and Torres (1993) showed that reading Braille is associated with expansion of the sensorimotor cortical representation of the reading finger. Even interhemispheric transfer of plasticity has been reported. Calford and Tweedale (1990) showed that in adult flying foxes a small peripheral denervation causes a receptive field expansion on the primary somatosensory cortex. This induced plasticity in one hemisphere was immediately mirrored in the contralateral hemisphere.

The results of these studies all indicate a functional unity between peripheral and central neural mechanisms which has clear implications for the study of reorganization processes after sensorimotor damage. Because such a unity is not at all specific for any kind of disorder but is a common characteristic of the nervous system, it can safely be assumed that in RSD also long-term central alterations result from prolonged peripherally distorted input. Such a centralization process may thus involve both spinal and cerebral structures. Cerebral involvement may be at the basis of poorly understood phenomena such as involuntary movements, initiation problems and the spreading of motor impairments far from the primarily affected area. It can be speculated that even the premotor and parietal association cortices can be dysregulated in persons with an enhanced central susceptibility to a distorted afference, causing all types of complex motor programming impairments. Such an interactionistic notion is in accordance with recent motor control theories (for extensive discussion see Mulder, 1993).

Psychopathological mechanisms

The possibility that RSD has a psychopathological aetiology continues to receive support in clinical practice and the medical literature (Ecker, 1990; Lang and Fahn, 1990). An interesting study (one of the few if not the only one with a prospective design) has been conducted by Zachariae (1964). One hundred patients with Dupuytren's contracture were operated on and then followed during the post-operative course. After a psychological

examination, 47 patients were classified as being at risk for developing RSD. The surgeon had no knowledge of this prediction. In 43 patients the prediction proved to be correct. Still, however remarkable this result may be, there is hardly any other support for a psychological basis of RSD. Bathia *et al.* (1993) reported 18 patients with causalgia and dystonia. They all suffered, besides the 'causalgia-dystonia syndrome', from vasomotor, sudomotor and trophic changes in combination with hyperpathia and allodynia. No one had a family history of dystonia or a history of neurological or psychiatric illness. All patients had normal cognitive and higher mental functions. Formal psychometry was carried out in nine cases and was normal. Lynch (1992) studied all the literature from the late 1800s to 1991 that contained any psychological information with respect to RSD. She concluded that, owing to definitional errors, semantic problems and other methodological shortcomings such as a lack of control groups, the currently available data are insufficient to draw inferences on the causality of psychopathological mechanisms in RSD.

However, there is agreement that behavioural and emotional issues in patients suffering from RSD are important and can be profound. This aspect has recently been underlined by Geertzen *et al.* (1994) who emphasized the importance of early stress management training in RSD. From a behavioural point of view, Fordyce (1976) and Vlaeyen *et al.* (1989) described that when pain becomes chronic the relationship between organic pathology and pain experience becomes less direct. Chronic pain can no longer be conceptualized as a pure sensory modality but should be considered as a 'pathological emotion'. In the biomedical model, nociception is controlled by somatic factors: a nociceptive stimulus is followed by a so-called respondent pain reaction. The value of the biomedical model is limited in the case of chronic pain. At this point, the direct relationship between a nociceptive stimulus and pain behaviour attenuates because an operant pain reaction has developed. An operant reaction is no longer related to the antecedent nociceptive stimulus but is controlled by the consequences of the exposed pain behaviour. In other words, merely anticipating the effect of the pain behaviour will trigger the behaviour without a direct relationship with a nociceptive stimulus. Hence, an operant reaction pattern must be regarded as the result of a learning process leading to a vicious circle of decreasing activity and increasing pain behaviour. In any patient with chronic pain, the question is not whether an operant reaction is present but rather to what extent this is the case. A treatment policy that strongly focuses on pain avoidance, particularly in the chronic stage of RSD, is a strong reinforcer of this vicious circle. Besides an operant aspect, there is also a cognitive-evaluative dimension to chronic pain. How is the pain interpreted by the patient? These interpretations are called 'causal attributions'. Causal attributions can be characterized by three dimensions: locus (is the cause of pain located inside or outside the person?), stability (is the cause of pain lasting or not?) and controllability (is the cause of pain subject to volitional control or not?). Based on these causal attributions the patient will try to reduce his suffering. In this perspective, it is important to prevent irrational or distorted inferences by means of education and cognitive treatment.

Conclusions and implications

Although RSD as a symptom complex has been recognized for over 100 years, it remains a controversial subject with many open questions regarding diagnostic criteria, pathophysiology and treatment. The diagnosis of RSD is primarily based on clinical grounds. Nevertheless, complementary technical investigations can be very helpful in making an

early diagnosis, excluding other pathologies and evaluating treatment. The three-phase bone scanning technique should be particularly mentioned.

The clinical picture of RSD stage I resembles an inflammatory reaction. It is, therefore, surprising that immunological data on RSD are scarce. This topic needs further investigation. Converging lines of research on the pathophysiology of RSD strongly suggest that, as a result of the adaptivity of the central nervous system to peripheral pathology, a process of centralization may occur in time. In the early stage, peripheral processes such as overproduction of toxic free radicals, sympathetic nervous system dysregulation and neurogenic inflammatory reactions predominate. In later stages, spinal and supraspinal processes seem to prevail. It is argued here that such a centralization process may be at the basis of both chronic pain and motor impairments in RSD. From this viewpoint, it can also be understood that some of the RSD-associated motor impairments may become irresponsive to sympathetic blocks and may spread to other parts of the body. Indeed, it has been convincingly demonstrated that a prolonged distortion of normal input patterns causes central adaptations in related neural networks. These central alterations of sensorimotor representation might be (in)directly responsible for complex motor programming impairments, e.g. initiation and coordination problems or the spreading of such loss of motor control to remote body parts.

In view of the considerations mentioned above, it seems essential to re-establish a normal afference to the central nervous system as early as possible. Therefore, early diagnosis and aggressive treatment of RSD in its initial stages are obligatory. Inflammatory reactions should be treated, e.g. with radical scavengers (such as mannitol or dimethylsulphoxide) or corticosteroids, trophic disturbances and vasospasms with sympathetic blocks and vasodilating medication, whereas pain and swelling should be reduced by analgetics (e.g. NSAID, calcitonine or anaesthetic blocks). Only when input can be normalized in an early stage, excitation of spinal and supraspinal centres might be prevented. Because in stage I of RSD complaints and symptoms are exercise-induced or dependent, one is inclined to prescribe physical rest to prevent exacerbation of inflammation. Physical therapy should be given without increasing pain and swelling. However, during later stages a regimen dictated by preventing pain perception may easily enhance the possibility of developing a chronic pain problem, characterized by a vicious circle of decreasing physical activity and increasing pain behaviour. Hence, stimulating activity during RSD stages II and III may help to prevent the development of such a vicious circle. Naturally, physical therapy should be well-planned with a focus on active rather than passive movements. In this way, normal proprioception is also promoted. At all costs, chronic disuse with the possibility of a virtual disappearance of the affected extremity from the normal body scheme should be prevented.

From a psychological viewpoint, it seems relevant to strengthen the patient's coping style and to reduce as many external stressful factors as possible. For this reason, psychological counselling can be useful. Moreover, a behaviourally trained psychologist can educate and train both the patients' family and the entire rehabilitation team to adapt their judgements and behaviour in such a way that normal use and experience of the affected extremity is reinforced whenever possible. It is only through a well-coordinated and theory-based rehabilitation strategy that patients in the more chronic stages of RSD may eventually prove to have a fair chance of recovery from the severe disabilities that often result.

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